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Acute Kidney Disease in Oncology: A New Concept to Enhance the Understanding of the Impact of Kidney Injury in Patients with Cancer

Matteo Floris[a] Francesco Trevisani[b] Andrea Angioi[a] Nicola Lepori[a, c] Mariadelina Simeoni[d] Gianfranca Cabiddu[a, c] Antonello Pani[a, c] Mitchell Howard Rosner[e]

[a]Nephrology, Dialysis and Transplantation Unit, Università degli Studi di Cagliari, G. Brotzu Hospital, Cagliari, Italy; [b]Division of Experimental Oncology, Urological Research Institute (URI), IRCCS San Raffaele Scientific Institute, Milan, Italy; [c]Medical Science Department, University of Cagliari, Cagliari, Italy; [d]Department of Translational Medical Sciences University of Campania "Luigi Vanvitelli", Naples, Italy; [e]Division of Nephrology, University of Virginia Health System, Charlottesville, VA, USA

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Abstract
Background: Cancer patients are prone to developing acute kidney disease (AKD), yet this phenomenon remains understudied compared to acute kidney injury (AKI). AKD, which often develops insidiously, can cause treatment interruptions, extended hospital stays, and increased mortality. ***Summary:*** This perspective article explores the intricate relationship between AKD and cancer, focusing on prevalence, risk factors, implications for anticancer therapy, and long-term outcomes, including chronic kidney disease progression. ***Key Messages:*** To emphasize the importance of early detection and intervention, this work advocates for increased research and awareness among clinicians to improve patient outcomes and manage healthcare burdens associated with AKD in cancer patients.

Introduction

Cancer patients are more susceptible to developing acute and chronic renal complications due to various factors, including the direct effects of malignancy, treatment-related toxicities, and comorbidities [1]. Renal impairment can cause interruptions in anticancer therapy, increased mortality rates, prolonged hospitalization, and higher healthcare costs [2]. While the prevalence and causes of acute kidney injury (AKI) in cancer patients have been extensively explored in oncology and nephrology [3, 4], renal alterations may develop insidiously in many cases and remain underrecognized when not fulfilling the AKI diagnostic criteria. These conditions, defined as acute kidney disease (AKD) [5], may be associated with worse clinical outcomes without increasing clinicians' awareness. In this paper, we aim to explore the complex relationship between AKD and cancer

Matteo Floris and Francesco Trevisani share the first authorship equally.
Antonello Pani and Mitchell Howard Rosner share the last authorship equally.

karger@karger.com
www.karger.com/kbr

Correspondence to:
Matteo Floris, matteo.floris@aob.it

patients, focusing on this condition's prevalence and risk factors, the implications for anticancer therapy, and the long-term outcomes, including CKD progression and increase in mortality and hospitalization.

Definitions of AKI and AKD

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines defined AKI as the presence of an increase in serum creatinine (SCr) by 50% within 7 days or by 0.3 mg/dL within 2 days or the presence of oliguria for more than 6 h [6]. AKD is defined as any alteration in kidney function and structure lasting less than 90 days from an initiating event. Since not all AKD conditions are the progression of AKI episodes, the current definition of AKD includes the presence within 3 months from a triggering event of AKI or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 or a decrease in GFR of more than 35% or an increase in SCr of more than 50% [5]. Outcomes over the 3 months include complete, partial, or non-recovery of renal function with the transition to chronic kidney disease (CKD) if GFR is persistently below 60 mL/min/1.73 m^2 [5].

Epidemiology of Acute and Subacute Kidney Disease in Cancer Patients

AKI poses a significant risk to cancer patients, increasing morbidity and mortality. Registry-based studies have consistently shown a higher incidence of AKI in this population than in non-cancer patients, with a one- and 5-year risk after a cancer diagnosis that can reach 17.5% and 27%, respectively. The incidence of AKI in cancer patients varies depending on factors such as the type and stage of cancer, treatment modalities, and hospitalization status and ranges from approximately 7 to 20% [3, 4]. Lastly, cancer patients with AKI have higher in-hospital mortality rates than those without AKI (12 vs. 0.9%) [7], emphasizing the critical impact of renal complications on patient outcomes.

Recently, a large federated cohort analysis of electronic alert (EA) data across a population of seven million individuals living in three high-income countries found 464,868 incident cases of AKD diagnosed using the KDIGO definition. The analysis was mainly focused on characterizing renal function recovery and 1-year mortality rate, according to various AKD definitions, based on the temporal interval (48 h, 7 days, 8–90 days) from the insult. The comorbidities in this population included diabetes, coronary heart disease, heart failure, stroke, peripheral arterial disease, and cancer (in 16.8–28.7% of various AKD subsets). Several important pieces of information came from this analysis. First, analyzing the 90-day interval from a renal insult lets us identify the highest number of AKD subjects. Second, AKD is associated with a 1-year mortality rate of 40%: this rate is nearly the same as observed when kidney injury was defined using exclusively AKI criteria. Third, a correlation between criteria used for AKD definition and percentage of recovery has been demonstrated: 16% of patients who developed AKD in 48 h do not recover, while the percentage increases to 25% when AKD was identified using a temporal interval of 90 days. Fourth, a substantial proportion of patients with recovery at 14 and 90 days subsequently deteriorated to a state of non-recovery: non-recovery deteriorations occurred in 44% and 30% of people who had apparent recovery at 14 and 90 days, respectively. Lastly, while events occurring in 48-h intervals are almost all detected in hospital settings, events occurring up to 7 days are more commonly identified in outpatient settings with all the associated limits, especially in a context where access to blood tests is limited. Taken together, these data confirm that focusing the attention only for 48 h or 7 days SCr changes in numerous clinical subsets, including cancer, might lead to no diagnosis and curing a significant amount of AKD patients who have the same risk of developing subsequent loss of renal function and mortality as their counterpart [8].

The incidence of AKD in cancer patients has not yet been evaluated in extensive studies. In a cohort of 509 patients treated with high-dose cisplatin due to head and neck squamous cell carcinoma, AKD and AKI occurred in 27.9% and 13.4% of patients. Furthermore, AKI but not AKD patients received a significantly lower cisplatin cumulative dose, mainly due to a modification in the CT scheme in those patients who developed AKI. AKD patients developed an estimated GFR (eGFR) decline more significant than 30% that persisted even 9 months after chemotherapy completion [9]. Clinical data from our personal experience in head and neck patients who underwent CRT showed an AKI incidence of 12.7% and an AKD incidence of 25.7%: hypertension, baseline eGFR, and therapy with renin-angiotensin-aldosterone system inhibitors proved to be significant factors associated with both AKI and AKD [10]. AKD has not been studied in patients undergoing immune checkpoint inhibitor (ICPi) treatment. A multicenter cohort analysis of 429 patients with ICPi-associated AKI showed that only 6 out of 10 patients experienced renal recovery, defined as a decrease in SCr to less than 1.5 times the baseline after 3 months; the early initiation of steroid therapy was associated with positive outcomes [11]. These data suggest that early recognition of acute renal alterations and prompt initiation of opportune therapy and monitoring strategies

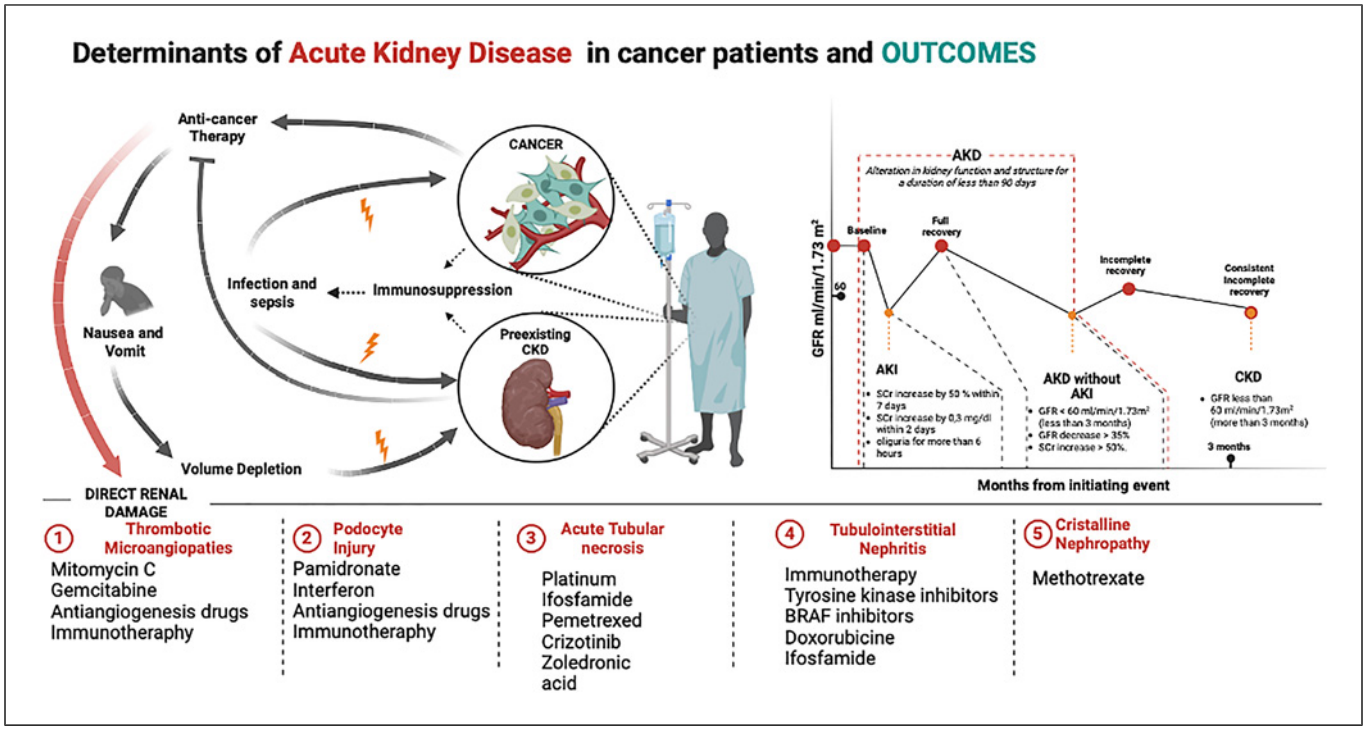

Fig. 1. Determinants of AKD in cancer patients and outcomes. CKD, chronic kidney disease; AKI, acute kidney injury; AKD, acute kidney disease. (Created with BioRender.com).

may limit exposure to nephrotoxic compounds and that many patients develop long-term renal complications after developing cancer therapy-related adverse events.

Causes of AKD in Cancer Patients

The pathogenesis of AKI and AKD in cancer patients is often multifactorial. Various insults, such as volume depletion, infection, and anticancer compounds, simultaneously contribute to renal damage by acting directly and creating an unfavorable milieu often sustained by preexisting CKD. CKD patients are more susceptible to renal insults such as hypovolemia and dehydration, which can occur due to reduced fluid intake and gastrointestinal losses from anticancer therapy-induced nausea, vomiting, and mucositis. Furthermore, infections and sepsis are additional triggers for AKI and AKD in cancer patients due to their risk of developing infections caused by a malignancy-induced immunosuppressive state and the effect of anticancer medications. Nephrotoxic agents, particularly numerous anticancer therapies, can directly damage every site of the nephron through various insults, including thrombotic microangiopathy (TMA), podocytopathy, acute tubular necrosis, tubulointerstitial nephritis, and crystalline nephropathy (Fig. 1). Besides the causes mentioned above, other factors contributing to AKI and AKD include tumor lysis syndrome, urinary tract obstruction, and exposure to radiocontrast agents.

Although AKI and AKD often coexist in cancer patients, studies have shown that up to half of AKD episodes occur without AKI [8, 9]. These episodes of AKD without AKI are critical since they are characterized by a slow increase in damage markers over weeks or months, often not sparking the attention of clinicians until renal function is severely impaired. The consequences can be significant and include interruption of anticancer therapy, increased rate of hospitalization, and CKD progression.

Role of Renal Biopsy in AKD Evaluation

Kidney biopsy is the gold standard for diagnosing, staging, and treating parenchymal kidney diseases. Its role in oncologic patients with AKD is slightly different from that of AKI since, in these patients, we must ask why the kidney function is not improving and whether the pathologic process is still active or scarring [12].

Before the term onconephrology was coined, kidney pathology recognized many kidney conditions that manifest as direct (e.g., drug toxicity, kidney infiltration) or indirect (e.g., IgA nephropathy) harm due to cancer or its treatment [13]. Recently, nephrologists have gradually increased their confidence in considering kidney biopsy in oncologic patients since this cohort's overall survival improved.

Every kidney structure, namely, vessels, glomeruli, tubules, and interstitium, can be harmed according to the type of neoplastic disease or its treatment. Unfortunately, there is still no data on the histological spectrum of lesions observed in AKD cohorts of oncologic patients. Similarly, data are scarce in the general population, but some have addressed a few indications [11, 14, 15]. According to these studies, in the general population, glomerular diseases represent most of the episodes (23%) [15], most of them ANCA-associated vasculitis (32%), lupus nephritis (16%), intra- or postinfectious glomerular diseases (7%), or paraprotein-related glomerular diseases (3%) [16]. Other causes are malignant hypertension (20%) and light-chain cast nephropathy (7%). Despite the ongoing process, there is a limited amount of interstitial fibrosis (55.2–64.9%) and tubular atrophy (59–65.3%), and there is a significant percentage of patients with reversible tubular lesions, such as acute tubular necrosis (19%) or acute interstitial nephritis (15%) [15]. Often, scarring is already established before the event, causing a persistent decline of kidney function (e.g., diabetes, hypertension) [16].

In cancer patients with persistent kidney dysfunction, biopsies are not just diagnostic but can also guide therapeutic decisions, helping clinicians determine whether to continue, withhold, or adjust therapy. Cytotoxic agents (e.g., cisplatin, carboplatin, ifosfamide, pemetrexed, methotrexate) are known to cause acute tubular necrosis, which leads to interstitial scarring and tubular atrophy if the insult is chronic. TMA has been reported with vascular endothelial growth factor inhibitors, mitomycin C, and gemcitabine.

A chapter apart is needed for ICPi (CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors), whose persistent kidney dysfunction is, in most cases, driven by acute interstitial nephritis. However, there are several case reports whose, after kidney biopsy, cause of the AKD was an ongoing, persistent, acute tubular necrosis [17] or more complex histological patterns such as lupus-like membranous nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, TMA, and AA amyloidosis; these patterns might follow a direct hit by ICPi or the antigen showering of the kidney structures secondary to tumor cell lysis [18]. Podocytopathy (primary focal and segmental glomerulosclerosis and minimal change disease) has also been described [19]. More sophisticated markers are emerging to differentiate ICPi-AIN from non-ICPi-AIN, like using anti-PD1 and anti-PD-L1 antibodies in kidney immunohistochemistry, which in >90% of cases mark positive for the lymphocyte infiltrate and the tubules, respectively [20].

Other indications to perform a kidney biopsy may be indicated in contexts of electrolyte disorders refractory to therapeutic intervention (e.g., hypokalemia, type I or II renal tubular acidosis), which may be secondary to AIN, tumoral infiltration of the parenchyma, or a direct insult against proximal (Fanconi's syndrome) or distal tubule as may be seen in light-chain proximal tubulopathy and cast nephropathy, respectively [20]. A kidney biopsy is crucial in diagnosing, prognosis, and treating multiple myeloma. Cast nephropathy refers to kidney damage caused by an overflow proteinuria due to a high burden of light chains produced by a large clone. This is why it is considered a defining event for myeloma. Other histological patterns are observed less frequently in multiple myeloma (e.g., monoclonal immunoglobulin deposition diseases, proliferative glomerulonephritis with monoclonal immunoglobulin deposits). Still, the pathogenetic insult is secondary to the chemical-physical characteristics of the monoclonal protein itself instead of its quantity. The concept of overflow proteinuria has prompted different therapeutic strategies in support of chemotherapy focused on the mechanical removal of light chains (e.g., plasmapheresis, high-cutoff hemodialysis) with ongoing, debated success [21]. Moreover, kidney biopsy is the only tool in diagnosing monoclonal gammopathy of renal significance. In these settings, demonstrating kidney damage due to monoclonal protein (with direct or indirect mechanism) is of the utmost importance since it should lead to a prompt beginning of treatment against the monoclonal clone beyond the usual oncohematological indications [22]. Table 1 summarizes the most frequent indications for renal biopsy in cancer patients with AKD.

The Rationale for AKD Evaluation in Oncology: Potential Implications for Clinical Practice and Research

The widespread application of KDIGO criteria for defining AKI in oncology has raised clinicians' awareness of the negative impacts of this condition on cancer patients. However, it is essential to consider that AKI does not encompass all acute kidney alterations since these may develop over a more extensive period, significantly impacting medium- and long-term outcomes. The definition of AKD might offer a broader perspective, including both transient and sustained acute renal disorders. From a clinical point of view, this approach might

Table 1. Indications for kidney biopsy in the setting of AKD in cancer patients

Delayed recovery of renal function after treatment with drugs known as cause of acute tubular necrosis (i.e., cisplatin, carboplatin, ifosfamide, pemetrexed, methotrexate)
AKD in patients treated with immunotherapy without rapid improvement after glucocorticoid treatment
AKD in patients treated with immunotherapy who showed signs of glomerular damage (i.e., microscopic hematuria, proteinuria, nephrotic syndrome)
AKD in multiple myeloma
AKD in patients with evidence of MGUS
AKD without evidence of prerenal and post-renal causes of kidney injury and obvious exposition to nephrotoxic drugs
AKD associated with proteinuria and/or glomerular microscopic hematuria
Electrolyte disorders refractory to therapeutic interventions (i.e., Fanconi's syndrome)

AKD, acute kidney disease; MGUS, monoclonal gammopathy of undetermined significance.

raise the clinicians' attention to the medium- and long-term consequences of AKD, including discontinuation or down-titration of anticancer agents and the development of CKD. A proactive medical approach is thus warranted even when a slight increase in renal damage markers occurs. It might include the early application of the KDIGO bundle and the application of specific strategies to limit the progression of renal damage. Due to the prolongation of therapeutic regimens, particularly in an older population affected by a rising number of comorbidities, identifying early markers of renal damage progression, such as AKD, is paramount to target the appropriate therapeutic response.

Research on AKD, particularly without AKI, is still in the early stages in multiple clinical fields, including onconephrology, with a limited understanding of its epidemiology, causes, pathophysiology, prevention, and treatment. AKD and its relationship with CKD is an emerging area of research requiring systematic exploration. Furthermore, more information is needed about the long-term effects of newer anticancer agents, including most immunotherapy drugs. AKD and its development and evolution are almost entirely unexplored in this setting. Since an urgent need exists for specific clinical trials, a reasonable approach, suggested by the Acute Disease Quality Initiative (ADQI), might include reanalyzing the existing datasets with a particular focus on AKD outcomes. Lastly, new databases and clinical trials focusing on AKI must include AKD data to establish and widely disseminate a definitive understanding of this condition and design studies that accurately measure early and long-term outcomes and assess specific interventions [5, 12].

Challenges of AKI and AKD Recognition in Cancer Patients: Strategies for Overcoming Obstacles

Apart from cases handled by top-level institutions, clinicians often struggle to identify acute kidney alterations, such as AKI and AKD. Most patients do not recognize these alterations until they have reached an advanced stage, which highlights the challenges in accurately diagnosing such conditions and perceiving the benefits of early intervention.

The primary challenge in the field is to improve oncological awareness about the clinical significance of AKD. Over 20 years ago, the ADQI proposed a unified definition of acute renal failure [23], which was later refined and staged in AKI [6] according to KDIGO criteria and AKD [5]. However, from an oncological perspective, acute kidney alterations are often reported and staged in clinical trials according to the Common Terminology Criteria for Adverse Events (CTCAE), updated in 2017 [24]. One of the limitations of this classification is that the intervention, which may include diagnostic and therapeutic procedures, is only indicated for SCr values exceeding 50% of upper laboratory limits. This criterion may classify conditions as "mild," even if the eGFR loss exceeds 50% of the baseline. Additionally, the first stage of renal injury often involves the renal functional reserve. It may lead to subclinical damage characterized by elevated stress biomarkers without an increase in SCr [25].

It is estimated that about 80% of patients who experience mild grade of AKI during recovery in the hospital are not aware of having been affected by an acute episode of renal damage, and, therefore, they will probably not see

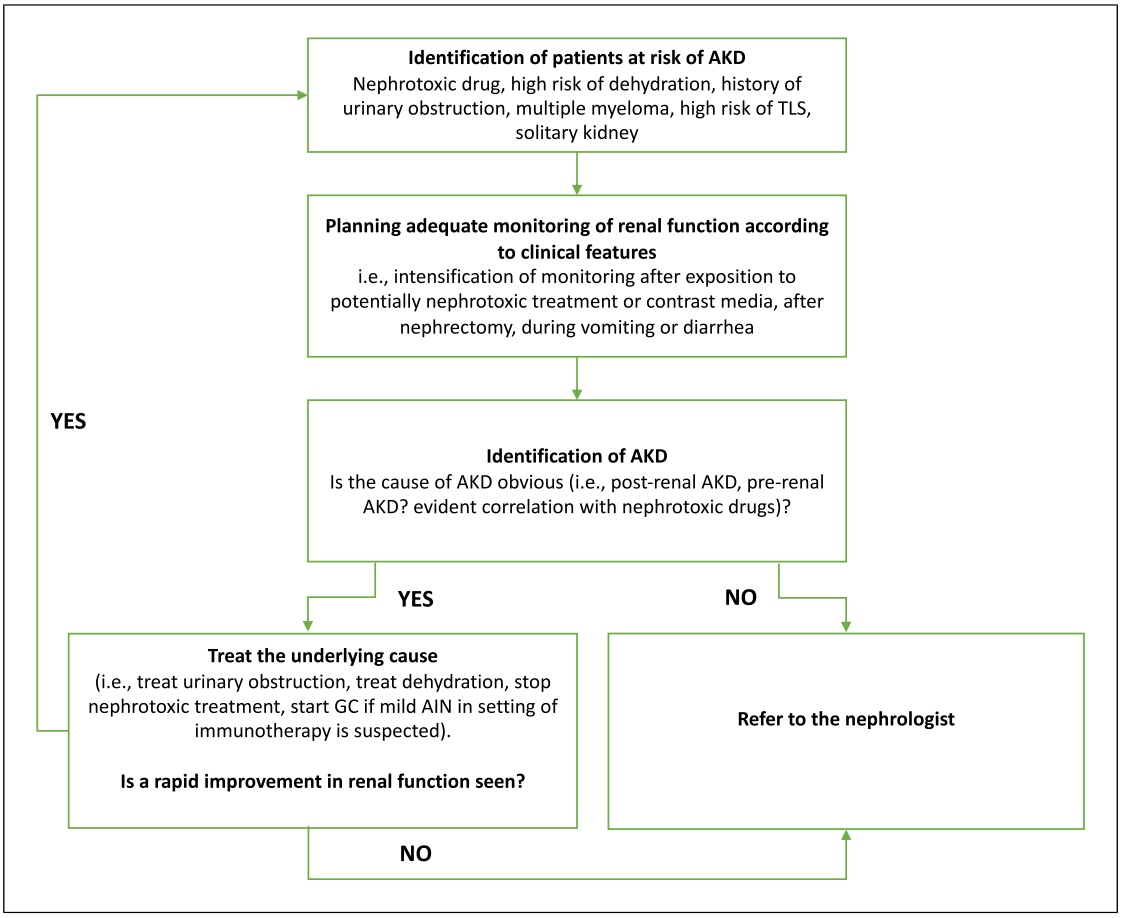

Fig. 2. Flowchart for assessment and initial management of AKD in non-nephrological setting. AKD, acute kidney disease; TLS, tumor lysis syndrome; GCs, glucocorticoids; AIN, acute interstitial nephritis.

a nephrologist in the following months after dismissal [26]. Surprisingly, patients who undergo transitory dialysis for an acute event during hospitalization will be followed by nephrologists in a percentage between 8% and 41% within 1 year of hospital discharge [27]. However, a non-negligible part of them will never restore their previous renal status due to nephron loss, endothelial injury, vascular damage, interstitial and tubular inflammation, fibrosis, and maladaptive repair mechanisms [28]. All these biological alterations will inevitably lead to a mild or severe grade of CKD due to the absence of tailored nephrological counseling able to treat the pathological condition promptly [29].

The second challenge is tracking renal abnormalities in patients who frequently undergo hospital admissions and various clinical diagnostic tests from different institutions. Prompt identification and application of therapeutic measures are crucial in diagnosing AKI based on critical care experience. To meet these requirements, some institutions use EAs, which have proven to be effective in diagnosing AKI and exerting clinical decision support aimed at improving the quality of care processes, enhancing patient safety, augmenting clinical care efficacy, and increasing provider and patient satisfaction [30]. While it was expected that clinical decision support would strengthen the quality of care and improve patient outcomes in acute care settings, current literature is inconsistent in providing evidence of such results [31]. This inconsistency is likely due to the need to adapt care processes to the quality and quantity of the information supplied by EAs. Furthermore, extending the diagnosis window to 90 days may pose additional challenges to managing AKD. However, there are some positive expectations for artificial intelligence tools that will soon be able to implement AKD care algorithms in inpatient and outpatient settings.

The third challenge pertains to the insufficient multidisciplinary management of cancer patients with AKI and AKD. This can lead to incorrect diagnosis, lack

of research on underlying causes – particularly when renal biopsy is needed – limited interventions, and ultimately, interruptions or underdosing of anticancer treatment. In recent years, many institutions have established onconephrology clinics and dedicated fellowship programs that have the potential to disseminate expertise in managing these conditions in cancer patients. The creation of these units should accomplish specific standards, including the proximity to the oncology and hematology wards, the availability of medical records across clinics, a shared (electronic) database, and the availability of specific tests, including Doppler interrogations and venous blood gas analysis [32]. The collective expertise in these clinics would help navigate the complexities of AKI management in the context of cancer and contribute to the advancement of the field through collaborative research and the development of evidence-based guidelines. The design of a practical flowchart for non-nephrologists, addressed to prompt identification and management of AKD in cancer patients, should be based on several fundamental steps, as described in Figure 2.

Conclusions

AKDs in cancer patients warrant urgent attention. While AKI has been extensively researched, it remains under-recognized despite its potential adverse outcomes and deserves a more vigilant and proactive approach to early detection and intervention. Moreover, a paradigm shift in research is essential, focusing on the epidemiology, causes, and long-term effects of AKD, especially concerning new anticancer therapies. Through collaborative research and clinical practice efforts, we can attempt to improve patient outcomes and reduce healthcare burdens associated with this condition in cancer patients.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization: Matteo Floris, Francesco Trevisani, Antonello Pani, and Mitchell Howard Rosner. Supervision: Antonello Pani and Mitchell Howard Rosner. Project administration: Matteo Floris, Antonello Pani, and Mitchell Howard Rosner. Writing – original draft: Matteo Floris, Francesco Trevisani, Andrea Angioi, Nicola Lepori, Antonello Pani, and Mitchell Howard Rosner. Writing – review and editing: Matteo Floris, Francesco Trevisani, Andrea Angioi, Nicola Lepori, Mariadelina Simeoni, Gianfranca Cabiddu, Antonello Pani, and Mitchell Howard Rosner. All authors have read and agreed to the published version of the manuscript.

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